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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,826	08/22/2001	Carol Shoshkes Reiss	REISS 1A	6205

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EXAMINER

MARSCHEL, ARDIN H

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 05/05/2003

7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/807,826

Applicant(s)

REISS ET AL.

Examiner

Ardin Marschel

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-15 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) 2 pages (1 sheet)
- 4) ☐ Interview Summary (PTO-413) Paper No(s). ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Minami et al. (1998).

Minami et al. disclose a method of regulating the permeability of the blood brain barrier (BBB) comprising administering to rats a composition comprising nitric oxide synthase-3 (NOS-3) regulating agent. Minami et al. Administer lipopolysaccharide (LPS) through intraperitoneal injection which causes increased permeability to the blood brain barrier during bacterial infection (i.e., a pathological condition) on page 36, left column, lines 8-10, by producing nitric oxide (NO). See Methods and page 39, left column, line 8. Minami et al. Administer amino guanidine and the L-arginine analog L-NG-Nitro-L-arginine methyl ester (L-NAME) which is a non-isozyme selective NOS inhibitor (See abstract and Methods.) 15 minutes (i.e., contemporaneously) and 1 hour after LPS which effectively reduces the increased permeability of the BBB caused by treatment with LPS. See Figure 3. Minami et al. therefore anticipates the above listed instant claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Minami et al. (1998), taken in view of Poduslo et al. (P/N 5,670,477).

The description of Minami et al. has been set forth above regarding the basic instant invention. Minami et al. do not teach of local administration of a composition comprising a NOS-3 regulating agent to regulate the BBB permeability.

Poduslo et al. describe methods of administering pharmaceutical compositions to increase the permeability of the BBB as in column 17, last paragraph. The methods include local administration comprised of inhalation (column 18, line 7) and injection into the brachial vein (column 25, line 24) for the purpose of limiting diffusion and breakdown of the pharmaceutical compound before it reaches its intended destination. Given that 1) Minami et al. describe methods of administering NOS-3 regulating agents which reduce the increased permeability of the BBB caused by administration of LPS, and 2) that Poduslo et al. describe local administration of pharmaceutical compounds for the

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purpose of increasing the permeability of the BBB, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to administer the permeability regulating agents of Minami et al. by inhalation or brachial artery injection in view of Poduslo et al. describing the benefits and thus motivating the practice of limiting diffusion and breakdown of a pharmaceutical compound thus resulting in the practice of the instant invention.

Claims 1, 4, 6, 7, and 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barna et al. (1996), taken in view of Friden (P/N 5,527,527).

Barna et al. describe a method for regulating the permeability of the BBB comprising administering to mice a composition comprising NOS-3 regulating agent. Barna et al. intranasally (i.e., locally) administer vesicular stomatis virus (VSV) to mice (See page 335, left column, last 2 lines) which disrupts the BBB caused by the increased levels of NO (See page 339, last 3 lines.) (i.e., a NOS-3 activator). Barna et al. also administer interleukin-12 (IL-12) to the VSV infected mice which increased levels of NO, as shown by the increased levels of nitrite (NO₂⁻), a stable end-product of NO (See page 332, left column, first full paragraph.), thus effectively increasing the permeability of the BBB. Barna et al. further describe that besides IL-12, IFN-gamma and TNF-alpha also activate NOS-3 to effectively increase the permeability of the BBB (See page 332, left column, first full paragraph.) to mediate the broad range of effects of both the innate and acquired immunity associated with infection (See page 335, right column, second full paragraph.).

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Barna et al. does not describe a method of regulating the permeability of the BBB by administering a composition comprising both a NOS-3 activator (or NO donor) and a neurologically active therapeutic compound or diagnostic compound.

Friden describes a method of administering across the BBB the OX-26 antibody (i.e., a diagnostic compound targeting molecule.) conjugated to (i.e., associated with) a neuropharmaceutical or diagnostic agent, where the antibody binds to a transferring receptor on brain capillary endothelial cells (See column 2, first paragraph.). Friden further describes that neuropharmaceutical agents conjugated to the antibody include cytokines and lymphokines (See column 3, line 31.).

Given that 1) Barna et al. describes that upon administration of IL-12, NOS-3 is activated to produce NO which in turn increased the permeability of the BBB, and 2) that Friden describes administering a conjugate formed by OX-26 antibody and a neuropharmaceutical compound such as an interleukin for the purpose of administering a therapeutic across the BBB, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention, to administer OX-26 antibody conjugated to an interleukin such as IL-12 so as to cross the BBB because Barna et al. describe the potential advantages of using IL-12 for its ability to enhance permeability of the BBB and its beneficial effects in the immune response. Although Friden describe the OX-26 antibody as it is able to cross the BBB, one of ordinary skill in the art would have been motivated to utilize IL-12 to further increase the permeability of the BBB thus resulting in the practice of the above listed instant claims.

No claim is allowed.

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Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703)308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703)308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703)308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (703)305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

May 2, 2003

Ardin U. Marschel
Ardin U. Marschel
Ph.D.